

What is claimed:

1. A method of treating or ameliorating an indication of the invention in an animal, including a human, comprising administering an effective amount of (A) a compound of 5 the formula I:



wherein:

a. Het is a five or six membered heterocycle having a first ring nitrogen and optionally, a second or third ring nitrogen, with the remaining ring atoms being carbon, oxygen, or 10 sulfur; provided that Het is not thiazole, imidazole, oxazole, or dihydro or tetrahydro analogs thereof;

b. Het can be substituted on carbon atoms with

1. one or more substituents independently selected from hydrogen, acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, 15 alkoxycarbonylalkyl, alkyl, alkylamino, (C₁-C₃)alkylenedioxy, allyl, amino, ω -alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), cycloalkyl, dialkylamino, halo, hydroxy, (C₂-C₆)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylthio, alkylsulfonyl, alkylsulfinyl, alkylsulfonamido, trifluoromethyl, morpholin-4-yl, 20 4-[C₆ or C₁₀]arylpiperidin-1-yl, 4-[C₆ or C₁₀]arylpiperazin-1-yl, thiomorpholin-4-yl, piperidin-1-yl, Ar* (wherein, consistent with the rules of aromaticity, Ar* is C₆ or C₁₀ aryl or a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two 25 atoms of N, each heteroaryl ring can be optionally fused to a substituted benzene, pyridine, pyrimidine, pyridazine, pyrazine, or (1,2,3)triazine (wherein the ring fusion is at a carbon-carbon double bond of Het)), Ar*-alkyl, Ar*-O, Ar*SO₂-, Ar*SO₂-, Ar*S-, Ar*SO₂NH-, Ar*NH, (N-Ar*)(N-alkyl)N-, Ar*C(O)-, Ar*C(O)NH-, Ar*NH-C(O)-, and (N-Ar*)(N-alkyl)N-C(O)-; or

30 2. two adjacent substitutions together with their ring carbons form a fused C₆ or C₁₀ aryl ring which aryl ring can be substituted as set forth below; or
3. two adjacent substitutions together with their ring carbons form a C₅-C₇ fused cycloalkyl ring having up to two double bonds including any fused double bond

of the Het group, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxy carbonyl, amino, aminocarbonyl, carboxy, fluoro, or oxo; or

4. two adjacent substitutions together with their ring carbons form a fused 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N; or

5. two adjacent substitutions together with their ring carbons form a fused five to eight membered fused heterocycle, wherein the ring fusion is at a carbon-carbon bond of Het, wherein the fused heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, oxygen, sulfur, or $S(O)_n$, wherein $S(O)_n$ is 1 or 2; and

c. Het can be substituted on ring nitrogen atoms with

1. hydrogen, alkyl, alkoxy carbonyl alkyl-, Ar^* , Ar^*alkyl -, $Ar^*C(O)alkyl$ -, $ArS^*(O)alkyl$ -, $Ar^*S(O)_2alkyl$ -, so long as the ring nitrogen atoms are not quaternized;

2. amino; or

3. at most one nitrogen with oxido (-O⁺) to form an N-oxide; and

d. Y is substituted on a ring carbon adjacent to the first or second ring nitrogens and is

1. hydrogen, oxo, alkyl, mercapto, alkylthio, amino, amino(C_1-C_5)alkyl, or

aminophenyl, wherein the amino of the latter three groups can be (a) substituted with

(a) Ar^* ,

(b) Ar^*Z -, $Ar^*alkyl-Z$ -, $Ar^*Z-alkyl$ -, $Ar^*amino-Z$ -, $Ar^*aminoalkyl-Z$ - or $Ar^*oxyalkyl-Z$ -, wherein Z is a carbonyl or $S(O)_2$ or

(c) formyl or alkanoyl,

2. $-NHC(O)(CH_2)_n-D-R^eR^f$, wherein D is oxygen, sulfur or nitrogen, wherein when D is nitrogen n is 0, 1 or 2, but when D is oxygen or sulfur n=1 or 2, and R^f is present only when D is nitrogen,

wherein

(a) R^e is

(1) Ar^* , or

(2) a group of the formula

Het⁸-wherein Het⁸ is independently the same as Het, or

5 (3) a C₃-C₈ cycloalkyl ring having up to one double bond with the proviso
that the carbon linking the cycloalkyl ring to D is saturated, which
cycloalkyl ring can be substituted by one or more alkyl-,
alkoxycarbonyl-, amino-, aminocarbonyl-, carboxy-, fluoro-, or oxo-
substituents, or

10 (4) hydrogen, (C₂-C₆)hydroxyalkyl, alkanoylalkyl, alkyl,
alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be
substituted with alkoxyimino), alkoxy carbonyl, Ar*, or Ar*-alkyl-;
and

15 (b) R^f is independently hydrogen, hydroxy(C₂-C₆)alkyl, alkanoylalkyl, alkyl,
alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be
substituted with alkoxyimino), alkoxy carbonyl, independently a group
Ar* or Ar*-alkyl;

wherein aryl or Ar* in addition to any substitutions specifically noted can be substituted
with one or more substituents selected from the group of acylamino,
acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxy carbonyl,
alkoxycarbonylalkyl, alkyl, alkylamino, (C₁-C₃)alkylenedioxy, alkylsulfonyl,

20 alkylsulfinyl, ω -alkylenesulfonic acid, alkylthio, allyl, amino, Ar*C(O)-,
Ar*C(O)NH-, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo,
trifluoromethyl, hydroxy, (C₂-C₆)hydroxyalkyl, mercapto, nitro, morpholin-4-yl,
thiomorpholin-4-yl, piperidin-1-yl, Ar*O-, Ar*-, Ar*-alkyl-, sulfamoyl, sulfonic
acid, 1-pyrrolidinyl, 4-[C₆ or C₁₀]aryl piperidin-1-yl and 4-[C₆ or
25 C₁₀]aryl piperazin-1-yl; and

heterocycles except those of Het or Ar*, can be substituted with, in addition to
substitutions specifically noted, one or more substituents selected from
acylamino, alkanoyl, alkoxy, alkoxy carbonyl, alkoxy carbonylalkyl, alkyl,
alkylamino, alkylsulfonyl, alkylsulfinyl, alkylthio, amino, Ar*C(O)-, Ar*O-,
30 Ar*-, Ar*-alkyl, carboxy, dialkylamino, fluoro, fluoroalkyl, difluoroalkyl,
hydroxy, mercapto, 4-[C₆ or C₁₀]aryl piperidin-1-yl, 4-[C₆ or C₁₀]aryl piperazin-1-
yl, (C₁-C₃)alkylenedioxy, oxo, sulfamoyl, and trifluoromethyl;

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or a pharmaceutically acceptable salt of said compounds.

2. The method of claim 1, wherein

a. Het is a five or six membered heterocycle having a first ring nitrogen and optionally, a second or third ring nitrogen, with the remaining ring atoms being carbon, oxygen, or sulfur; provided that Het is not thiazole, imidazole, oxazole, or dihydro or tetrahydro analogs thereof;

b. Het can be substituted on carbon atoms with

1. one or more substituents independently selected from hydrogen, acylamino,

10 alkanoyl, alkanoylalkyl, alkoxy, alkoxy carbonyl, alkoxy carbonylalkyl, alkyl, alkylamino, amino, ω -alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), cycloalkyl, dialkylamino, halo, hydroxy, (C₂-C₆)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylthio, alkylsulfonyl, alkylsulfinyl, alkylsulfonamido, trifluoromethyl, morpholin-4-yl, thiomorpholin-4-yl, 4-[C₆ or C₁₀]arylpiperidin-1-yl, 4-[C₆ or C₁₀]arylpiperazin-1-yl, piperidin-1-yl, Ar* {wherein, consistent with the rules of aromaticity, Ar* is C₆ or C₁₀ aryl or a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring can be optionally fused to a substituted benzene, pyridine, pyrimidine, pyridazine, pyrazine, or (1,2,3)triazine (wherein the ring fusion is at a carbon-carbon double bond of Het)}, Ar*-alkyl, Ar*-O, Ar*SO₂-, Ar*SO-, Ar*S-, Ar*SO₂NH-, Ar*NH, (N-Ar*)(N-alkyl)N-, Ar*C(O)-, Ar*C(O)NH-, Ar*NH-C(O)-, and (N-Ar*)(N-alkyl)N-C(O)-; or

2. two adjacent substitutions together with their ring carbons form a fused C₆ or C₁₀ aryl ring which aryl ring can be substituted as set forth below, or

3. two adjacent substitutions together with their ring carbons form a C₅-C₇ fused cycloalkyl ring having no double bonds except any fused double bond of the Het group, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxy carbonyl, amino, aminocarbonyl, carboxy, fluoro, or oxo; and

c. Het can be substituted on ring nitrogen atoms with

1. hydrogen, alkyl, alkoxy carbonyl alkyl-, Ar*, Ar*alkyl-, Ar*C(O)alkyl-, ArS*(O)alkyl-, Ar*S(O)₂alkyl-, so long as the ring nitrogen atoms are not quaternized;

2. amino; or

5 3. at most one nitrogen with oxido (-O⁺) to form an N-oxide; and

d. Y is substituted on a ring carbon adjacent to the first or second ring nitrogens and is

10 1. hydrogen, oxo, alkyl, mercapto, alkylthio, amino, amino(C₁-C₅)alkyl, or aminophenyl, wherein the amino of the latter three groups can be (a) substituted with

(a) Ar*,

(b) Ar^{*}-Z-, Ar^{*}-alkyl-Z-, Ar^{*}-Z-alkyl-, Ar^{*}-amino-Z-, Ar^{*}-aminoalkyl-Z- or Ar^{*}-oxyalkyl-Z-, wherein Z is a carbonyl or S(O)₂ or

(c) formyl or alkanoyl,

15 2. -NHC(O)(CH₂)_n-D-R⁶R^f, wherein D is oxygen, sulfur or nitrogen, wherein when D is nitrogen n is 0, 1 or 2, but when D is oxygen or sulfur n=1 or 2, and R^f is present only when D is nitrogen, wherein

(a) R⁶ is

(1) Ar*,

20 (2) a group of the formula

Het⁸-

wherein Het⁸ is independently the same as Het,

25 (3) a C₃-C₈ cycloalkyl ring having up to one double bond with the proviso that the carbon linking the cycloalkyl ring to D is saturated, which cycloalkyl ring can be substituted by one or more alkyl-, alkoxy carbonyl-, amino-, aminocarbonyl-, carboxy-, fluoro-, or oxo- substituents, where multiple substituents are located on different carbon atoms of the cycloalkyl ring, except in the case of alkyl, alkoxy carbonyl, and fluoro substituents, which can be located on the same or different carbon atoms; or

30 (4) hydrogen, (C₂-C₆)hydroxyalkyl, alkanoylalkyl, alkyl, alkoxy carbonyl alkyl, alkenyl, carboxyalkyl (which alkyl can be

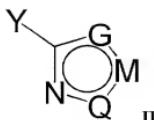
substituted with alkoxyimino), alkoxycarbonyl, Ar*, or Ar*-alkyl-; and

(b) R^f is independently hydrogen, hydroxy(C₂-C₆)alkyl, alkanoylalkyl, alkyl, alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkoxyimino), alkoxycarbonyl, independently a group Ar* or Ar*-alkyl;

wherein aryl or Ar* in addition to any substitutions specifically noted can be substituted with one or more substituents selected from the group of alkyl, amino, dialkylamino, 1-pyrrolidinyl, 4-[C₆ or C₁₀]arylpirazin-1-yl, 4-[C₆ or C₁₀]arylpiridin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl; and

heterocycles except those of Het or Ar*, can be substituted with, in addition to substitutions specifically noted, one or more substituents selected from acylamino, alkanoyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, alkylsulfonyl, alkylsulfinyl, alkylthio, amino, Ar*C(O)-, Ar*O-, Ar*-, Ar*-alkyl, carboxy, dialkylamino, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, 4-[C₆ or C₁₀]arylpiridin-1-yl, 4-[C₆ or C₁₀]arylpirazin-1-yl, (C₁-C₃)alkylenedioxy, oxo, sulfamoyl, and trifluoromethyl; or a pharmaceutically acceptable salt of said compounds.

20 3. The method of claim 1, wherein Het-Y is



wherein G, M, and Q are selected from the group consisting of O, S, C-R^h, C-Rⁱ, and N-R^g, with the proviso that only one of G or Q can be O or S,

a. wherein R^g is

(1) hydrogen, alkyl, alkoxycarbonylalkyl-, Ar*, Ar*-alkyl-, Ar*C(O)alkyl-, Ar*S(O)alkyl-, or Ar*S(O)₂alkyl-, so long as the ring nitrogen atoms are not quaternized; or

(2) amino or oxido (wherein N-R^g forms an N-oxide) and

b. wherein R^h or Rⁱ are

(1) independently selected from hydrogen, acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxy carbonyl, alkoxy carbonylalkyl, alkyl, alkylamino, (C₁-C₃)alkylenedioxy, allyl, amino, ω -alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), cycloalkyl, dialkylamino, halo, hydroxy, (C₂-C₆)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylthio, alkylsulfonyl, alkylsulfinyl, alkylsulfonamido, trifluoromethyl, morpholin-4-yl, 4-[C₆ or C₁₀]arylpiperidin-1-yl, 4-[C₆ or C₁₀]arylpiperazin-1-yl, thiomorpholin-4-yl, piperidin-1-yl, Ar*, Ar*-alkyl, Ar*-O, Ar*SO₂, Ar*SO-, Ar*S-, Ar*SO₂NH-, Ar*NH, (N-Ar*)(N-alkyl)N-, Ar*C(O)-, Ar*C(O)NH-, Ar*NH-C(O)-, and (N-Ar*)(N-alkyl)N-C(O)-;

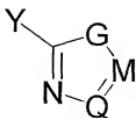
(2) R^h and Rⁱ where adjacent, together with their ring carbons form a C₅-C₇ fused cycloalkyl ring having up to two double bonds including the fused double bond of the Het group, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl-, alkoxy carbonyl-, amino-, aminocarbonyl-, carboxy-, fluoro-, or oxo- substituents, except in the case of alkyl, alkoxy carbonyl, and fluoro substituents, which can be located on the same or different carbon atoms;

(3) R^h and Rⁱ where adjacent, together with their ring carbons form a fused C₆ or C₁₀ aryl ring;

(4) R^h and Rⁱ where adjacent, together with their ring carbons form a fused five to eight membered fused heterocycle, wherein the ring fusion is at a carbon-carbon bond of Het, wherein the fused heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, oxygen, sulfur, or S(O)n, wherein S(O)n is 1 or 2; or

(5) R^h and Rⁱ where adjacent, together with their ring carbons form a fused 5- or 6-membered heteroaryl ring containing at least one and up to three atoms of N for the 6-membered fused heteroaryl rings and from one to three atoms of N or one atom of O or S and zero to two atoms of N for the 5-membered fused heteroaryl rings.

4. The method of claim 3, wherein Het-Y is



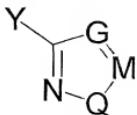
wherein G is O, S, N-R^g,

M is N or C-R^h, or

Q is N or C-Rⁱ.

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5. The method of claim 3, wherein Het-Y is



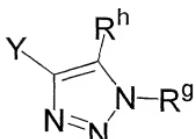
wherein G is N or C-R^h,

M is N or C-Rⁱ; and

Q is O, S, or N-R^g.

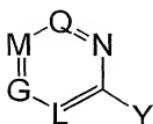
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6. The method of claim 3, wherein Het-Y is



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7. The method of claim 1, wherein Het-Y is



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wherein Q, M, G and L are independently N',C-R^j, C-R^k, C-R^l, or C-R^m, with the proviso that there are 1 to 3 N atoms in the ring, wherein

R^j, R^k, R^l and R^m are

a. independently selected from hydrogen, acylamino, acyloxyalkyl, alkanoyl,

5 alkanoylalkyl, alkenyl, alkoxy, alkoxy carbonyl, alkoxy carbonyl alkyl, alkyl, alkylamino, (C₁-C₃)alkylenedioxy, allyl, amino, ω -alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), cycloalkyl, dialkylamino, halo, hydroxy, (C₂-C₆)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylthio, alkylsulfonyl, alkylsulfinyl, trifluoromethyl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, Ar*, Ar*-alkyl, Ar*-O, Ar*SO₂-, Ar*SO-, Ar*S-, Ar*SO₂NH-, Ar*NH, (N-Ar*)(N-alkyl)N-, Ar*C(O)-, Ar*C(O)NH-, Ar*NH-C(O)-, and (N-Ar*)(N-alkyl)N-C(O)-; or

15 b. where two of R^j, R^k, R^l or R^m are adjacent, together with their ring carbons form a C₅-C₇ fused cycloalkyl ring having up to two double bonds including the fused double bond of the Het group, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl-, alkoxy carbonyl-, amino-, aminocarbonyl-, carboxy-, fluoro-, or oxo- substituents, wherein multiple substituents are located on different carbon atoms of the cycloalkyl ring, except in the case of alkyl, alkoxy carbonyl, and fluoro substituents, which may be located on the same or different carbon atoms; or

20 c. where two of R^j, R^k, R^l and R^m are adjacent, together with their ring carbons form a fused C₆ or C₁₀ aryl; or

25 d. where two of R^j, R^k, R^l and R^m are adjacent, together with their ring carbons form a fused five to eight membered fused heterocycle, wherein the ring fusion is at a carbon-carbon bond of Het, wherein the fused heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, oxygen, sulfur, or S(O)_n, wherein n is 1 or 2; or

30 e. where two of R^j, R^k, R^l and R^m are adjacent, together with their ring carbons form a fused 5- or 6-membered heteroaryl ring containing at least one and up to three atoms of N for the 6-membered fused heteroaryl rings and from one to three atoms of N or one atom of O or S and zero to two atoms of N for the 5-membered fused heteroaryl rings.

8. The method of claim 7,

a. wherein L is N;

b. G is C-R^j;

c. M is C-R^k;

5 d. Q is C-R^l; and

e. Y is amino, amino(C₁-C₅)alkyl, or aminophenyl, wherein the amino of all three groups can be substituted with

(1) Ar^{*},

(2) Ar^{*}-Z-, Ar^{*}-alkyl-Z-, Ar^{*}-Z-alkyl-, Ar^{*}-amino-Z-, Ar^{*}-aminoalkyl-Z- or 10 Ar^{*}-oxyalkyl-Z-, wherein Z is a carbonyl or S(O)₂ or

(3) formyl or alkanoyl.

9. The method of claim 7,

a. wherein L and Q are N;

15 b. G is C-R^j;

c. M is C-R^k; and

d. Y is amino, amino(C₁-C₅)alkyl, or aminophenyl, wherein the amino of all three groups can be substituted with

(1) Ar^{*},

(2) Ar^{*}-Z-, Ar^{*}-alkyl-Z-, Ar^{*}-Z-alkyl-, Ar^{*}-amino-Z-, Ar^{*}-aminoalkyl-Z- or 20 Ar^{*}-oxyalkyl-Z-, wherein Z is a carbonyl or S(O)₂ or

(3) formyl or alkanoyl.

10. The method of claim 3,

25 a. wherein Q is N;

b. G is N-R^g;

c. M is C-R^h; and

d. Y is amino, amino(C₁-C₅)alkyl, or aminophenyl, wherein the amino of all three groups can be substituted with

30 (1) Ar^{*},

(2) Ar^{*}-Z-, Ar^{*}-alkyl-Z-, Ar^{*}-Z-alkyl-, Ar^{*}-amino-Z-, Ar^{*}-aminoalkyl-Z- or Ar^{*}-oxyalkyl-Z-, wherein Z is a carbonyl or S(O)₂ or

(3) formyl or alkanoyl.